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REVIEW ARTICLE

Biological predictors of chemotherapy-induced peripheral neuropathy (CIPN): MASCC neurological complications working group overview

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating condition associated with a number of chemotherapeutic agents. Drugs commonly implicated in the development of CIPN include platinum agents, taxanes, vinca alkaloids, bortezomib, and thalidomide analogues. As a drug response can vary between individuals, it is hypothesized that an individual's specific genetic variants could impact the regulation of genes involved in drug pharmacokinetics, ion channel functioning, neurotoxicity, and DNA repair, which in turn affect CIPN development and severity. Variations of other molecular markers may also affect the incidence and severity of CIPN. Hence, the objective of this review was to summarize the known biological (molecular and genomic) predictors of CIPN and discuss the means to facilitate progress in this field.

Keywords Chemotherapy-induced peripheral neuropathy · CIPN · Neuropathy

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN), a common side effect of anti-neoplastic agents, significantly decreases quality of life (QOL) in patients with cancer. CIPN symptoms include numbness, tingling, and pain especially in the hands and feet. This in turn is associated with an inability to complete activities of daily living and with falling [1]. Development of CIPN may lead to dose modifications, decreased patient adherence, and treatment interruptions or discontinuation, thereby potentially impacting oncologic outcomes negatively. Those with CIPN also report increased unemployment and decreased annual income, further demonstrating the negative impact that CIPN can have on patients [2].

A meta-analysis involving over 4000 patients estimated CIPN prevalence to be about 68% by the end of the first month of chemotherapy and 30% at 6 months [3]. Drugs commonly implicated in the development of CIPN include platinum drugs, taxanes, vinca alkaloids, bortezomib, and thalidomide analogues.

Since the response to the same drug can vary between individuals, it is hypothesized that a patient's specific genetic variants could impact the regulation of genes involved in drug pharmacokinetics (PK), ion channel functioning, neurotoxicity, and DNA repair, which may in turn affect CIPN development and severity. The goal of this manuscript was to summarize the known biological (molecular and genomic) predictors of CIPN and discuss means to facilitate progress in the understanding and eventual management of CIPN.

Demographic and clinical predictors of CIPN

While there are established clinical risk factors for CIPN, none accurately predicts the severity of CIPN that an individual patient will have [4]. Cumulative dose is a strong risk factor for the development of CIPN with most neurotoxic anti-neoplastic drugs. Patients of older age may be more at risk for developing neurotoxicity [5–7]; however, other studies have not found age to be associated with greater CIPN incidence [8, 9]. These differing results may be due to confounding comorbidities. Obese cancer patients with CIPN experience higher levels of neuropathy burden [10]. Diabetic patients report a higher grade of CIPN, particularly with taxanes while patients with autoimmune diseases report less severe CIPN [6]. African-Americans have a higher incidence of CIPN following taxane treatment in comparison with other racial groups [11].

Pathophysiology and biological predictors of CIPN Table 1 summarizes the mechanisms of action of chemotherapeutic agents and reported genetic polymorphisms associated with CIPN. The molecular targets and pathways of CIPN are described in Fig. 1.

Platinum compounds Platinum compounds interfere with tumor cell proliferation, resulting in damage to non-dividing, post-mitotic peripheral neural tissue. This damage may be associated with sensory neuropathy with anterograde axonal degeneration, first described for cisplatin concentrations in tissue collected posthumously [12, 45]. Whether this is true for systemic concentrations is less well understood. In addition to chronic neuropathy, acute neuropathy presenting as cold-induced dysesthesia is unique for oxaliplatin and is thought to be related to the rapid generation of oxalate metabolites [12].

Indirect evidence indicates that neuropathy may be attributable to systemic platinum drug PK. It is suggested that increased fractionation of cisplatin in the bleomycin, etoposide, and cisplatin (BEP) regimen may reduce neurotoxicity with the 3-day regimen producing less acute and late sensory neuropathy than the 5-day with equivalent anti-cancer efficacy [46, 47].

Preclinical studies on the association between drug transporters and oxaliplatin-induced neuropathy in mice with genetic knockout of the organic cation transporter 2 (OCT2) strongly suggest that platinum accumulation is related to the activity of this transporter [48], suggesting that any indirect association between systemic concentrations and neuropathy would likely have to account for the magnitude of uptake transport into the dorsal root ganglion (DRG). Dasatinib is being investigated for its role in minimizing CIPN as it inhibits the activity of OCT2, which could decrease oxaliplatin uptake in the DRG [49]. However, a population-pharmacokinetic model did not detect any association between PK parameters of the parent compound or the free oxaliplatin concentrations and neuropathy incidence [50]; other small pilot studies have also not detected a relationship [51, 52]. Yet, in a randomized trial of reduced glutathione (GSH), co-administration, decreased neuropathy incidence, and increased oxaliplatin clearance were reported [53].

A number of aberrations identified as potential future therapeutic targets include several single nucleotide polymorphisms (SNPs) such as *ERCC1*, *ERCC2*, *XRCC1*, *CCNH*, *GPX7*, and *ABCC4*, which may play critical roles in neurotoxicity, as described in Table 1 and Fig. 1 [13–19]. One genomically targeted therapeutic intervention focuses on the protein, apurinic/apyrimidinic endonuclease (APE-1). APE-1 is critical in the DNA base excision repair pathway and oxidative stress response, thereby mitigating chemotherapy-induced neuronal DNA damage, especially from platinum agents [33]. Early phase clinical trials are underway to enhance anti-oxidant effects of APE-1 and inhibit damaging signals such as ERK-1/2 [54]. Early studies investigating the drug, APX3330, suggest a neuroprotective benefit similar to

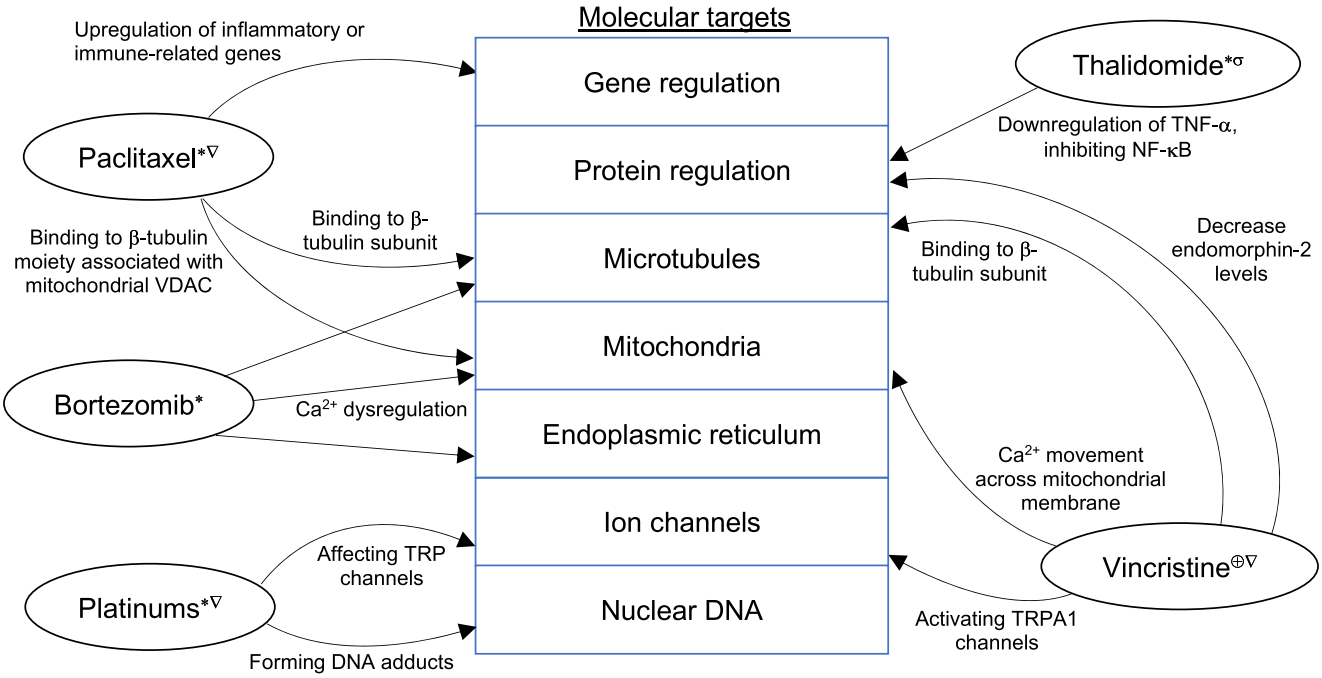

Figure 1 Molecular targets and pathways of CIPN. Affected neurons: dorsal root ganglion (∗); sensory neurons (∇); motor neurons (⊕); central projections of primary afferent neurons (σ). Abbreviations: *VDAC* voltage-dependent anion channels, *Ca2+* calcium ions, *TRP* transient receptor potential

the genetic APE-1 overexpression. This is achieved without minimizing chemotherapeutic efficacy by reducing redox signaling and improving DNA repair in sensory neurons [33].

Taxanes

Taxanes, which are spindle poisons, accumulate in the soma of sensory neurons of dorsal root ganglia. A retrograde "dying back" process is commonly observed, which typically starts at distal nerve endings, and is subsequently associated with the Schwann cell, neuronal body, or axonal transport changes. This sequence of alterations is believed to contribute to neurotoxicity. Genomic predictors of paclitaxel- and docetaxel-associated neuropathy are shown in Table 1.

The genetic prediction of paclitaxel-induced peripheral neuropathy has been extensively studied and recently reviewed [55]. Though candidate SNPs in cytochrome P450 (CYP) *CYP2C8* [21], *ABCB1* [21, 22], and *TUBB2A* [22] have been associated with neuropathy, none have been validated for use in clinical care due to inconsistent replication. Strong evidence links paclitaxel PK to the incidence of peripheral neuropathy [20, 56], including a randomized clinical trial demonstrating that exposure-guided paclitaxel dosing significantly reduces peripheral neuropathy incidence [57]. This PK association likely explains the reported associations for the putatively low-activity *CYP2C8*3* variant described above and the increased risk of paclitaxel-induced neuropathy in patients receiving the strong CYP2C8 inhibitor, clopidogrel [58, 59]. Genome-wide association studies (GWAS) have identified candidates for attempted replication, including SNPs in *FGD4* [23] and *EPHA5* [21]. SNPs in several EPHA genes including *EPHA4*, *EPHA5*, and *EPHA6* [1, 5] have been associated with paclitaxel-induced neuropathy, strongly suggesting this gene family is involved in neuropathy predisposition [60]. Many SNPs discovered via GWAS have been in genes involved in neurodevelopment, particularly those associated with hereditary neuropathy conditions [61] including *ARHGEF10* [24]. Other SNPs reported from GWAS have not been independently replicated [11, 34, 62–65]. Preclinical studies indicate that nilotinib may reduce paclitaxel-induced peripheral neuropathy through a non-competitive mechanism that allows paclitaxel to effectively attack cancer cells while inhibiting the solute carrier organic anion-transporting polypeptide B2 (*OATP1B2*). Suppression of *OATP1B2* activity was found to minimize peripheral neuropathy [66].

Few pharmacogenetic studies have been conducted for docetaxel-induced peripheral neuropathy. Candidate SNPs in *ABCB1* [25, 26] and *GSTP1* [25, 27] have been reported, but not yet validated [67]. The only completed GWAS reported a variant in *VAC14* that increased neuropathy risk and was confirmed to decrease neurite branching in vitro and increase mouse neuropathy sensitivity in *VAC14* knockout studies [68, 69]. There have been no pharmacogenetic studies of neuropathy caused by albumin-bound paclitaxel (nab-paclitaxel) or cabazitaxel.

Table 1 Reported genetic polymorphisms associated with chemotherapy-induced peripheral neuropathy

Agent	Mechanism	Gene (-SNP)	Functional pathway	Reference
Platinum	Interfere with tumor cell proliferation by forming DNA-platinum adducts that accumulate in the DRG and in peripheral neurons.	ERCC1	DNA repair	[13]
		ERCC2	DNA repair	[14, 15]
		XRCC1	Cell cycle progression, RNA transcription, DNA repair, and possibly repair after platinum induced damage to DRG	[15, 16]
		CCNH	Oxidative damage protection	[17, 18]
		GPX7	Transporter enzyme	[19]
		ABCC4	Glutathione	[19]
Paclitaxel	Stabilization of microtubules and inhibition of depolymerization, forming abnormal microtubule bundles in the cytoplasm and producing mitotic spindle disruption and apoptosis [21].	CYP2C8	Metabolizes paclitaxel	[21]
		ABCB1	Cellular and systemic drug efflux transporter	[21, 22]
		TUBB2A	Molecular target for paclitaxel	[22]
		FGD4	Myelin production	[23]
		EPHA4, 5, 6	Nervous system development / repair	[1, 5, 21]
		ARHGEF10	Neurodevelopment	[24]
Docetaxel	Stabilization of microtubules and inhibition of depolymerization, forming abnormal microtubule bundles in the cytoplasm and producing mitotic spindle disruption and apoptosis.	ABCB1	Cellular and systemic drug efflux transporter	[25, 26]
		GSTP1	Drug conjugation and detoxification	[25, 27]
		VAC14	Neurodevelopment	[53, 54]
Vinca alkaloids	Promote disassembly of microtubules by binding to tubulin during S phase and preventing microtubule polymerization, disrupting mitotic spindle formation in M phase, and rendering cell unable to divide.	CEP72	Microtubule formation	[29–32]
		CYP3A5	Vincristine metabolism	[33–40]
Bortezomib	Indirectly polymerize tubulin, causing microtubule stabilization, axonal transport inhibition, and G2-M phase cell cycle arrest.	CTLA4 rs4553808	Immune function	[41]
		PSMB1 rs1474642	Drug binding	[41]
		PKNOX1-21q22.3	Severe bortezomib-IPN	[42]
		CDH13, DCC, TENM3: 4q34.3-rs6552496, 5q14.1-rs12521798, 16q23.3-rs8060632, 18q21.2-rs17748074	Unknown: intergenic	[39]
Thalidomide	Inhibit production of IL-6 (growth factor), blocks the cell growth-stimulating CD147/MCT1 protein complex from binding to cereblon, activate apoptotic pathways through caspase 8-mediated cell death, and activates T cells to produce IL-2 augmenting NK-dependent cytotoxicity.	ABCA1	Neuroinflammation, neurodegeneration	[43]
		ICAM1	Myelinogenesis, nerve regeneration	[43]
		PPARD	Promote mitochondrial biogenesis	[43]
		SERPINB2	Proteostasis, neuro-cytoprotection	[43]
		SLC12A6	K & Cl cotransporter	[43]
		GSTT1	Drug conjugation and detoxification	[44]

Vinca alkaloids

Vinca alkaloids, such as vincristine and vinblastine, block microtubule polymerization, consequently disrupting mitotic spindle formation and rendering the cell unable to divide. Mutations in *CEP72* and *CYP3A5* have been most extensively studied as factors possibly influencing the development of vincristine-induced neuropathy. Studies have demonstrated that SNPs that reduce *CEP72* expression may lead to the development of neuropathy in patients on vincristine [29, 30], although subsequent studies were unable to consistently reproduce this finding [31, 32]. Vincristine is primarily metabolized by CYP3A4 and 3A5. Polymorphisms of *CYP3A5* are common, with the *CYP3A5*1/*1* genotype being associated with expression of *CYP3A5* and is more common in African-Americans. The *CYP3A5*3/*3* genotype is associated with non-expression of *CYP3A5* and is more common in Caucasians [35, 36]. Early studies suggested a possible association between *CYP3A5* genotypes and vincristine-induced peripheral neuropathy [34, 37]. The *CYP3A5*1/*1* genotype is associated with a lower incidence of neuropathy compared with the *CYP3A5*3/*3* genotype [38]. However, others have also reported no effect of *CYP3A5* genotype on the development of neuropathy [33, 39]. Early evidence suggests that vincristine PK may be associated with neuropathy [18]; however, validation has been challenging [35, 40].

Bortezomib

The proteasome inhibitor, bortezomib, promotes G2-M cell cycle arrest and apoptosis through the disruption of the ubiquitin-proteasome pathway which degrades dysfunctional intracellular proteins. Subcutaneous administration of bortezomib has been found to greatly reduce reported bortezomib-induced peripheral neuropathy in comparison with intravenous administration, as well as the reduction of other adverse effects [37]. Despite the same treatment efficacy, the prevalence of peripheral neuropathy in the population treated with subcutaneous injection is 38% in comparison with 53% in those treated with intravenous bortezomib [37]. The exact mechanism of bortezomib-induced peripheral neuropathy is unknown. SNPs in *CTLA4 rs4553808* and *PSMB1 rs1474642* have been reported to be associated with bortezomib-induced neuropathy [41]. A GWAS study identified 4 new loci that were associated with bortezomib-induced peripheral neuropathy, found in genes involved in the development and function of the nervous system including *CDH13*, *DCC*, and *TENM3* [39]. Another GWAS study identified a gene locus mapping to *PKNOX1* and in close proximity to *CBS* at 21q22.3 that was correlated with the severe bortezomib-induced toxicity [42]. However, additional studies to validate these findings are needed prior to establishing these genes for study as therapeutic targets.

Thalidomide

Thalidomide, an immunomodulatory agent, prevents cell proliferation through inhibition of angiogenesis as well as alteration of the immune system through multiple mechanisms including inhibition of interleukin (IL)-6 production, activation of caspase 8–mediated apoptosis, and increased production of IL-2 through T cell activation. Based on a meta-analysis, thalidomide-related peripheral neuropathy has been described in 63.5% of patients [3]. Several SNPs have been found to be associated with thalidomide-related peripheral neuropathy: *ABCA1*, *ICAM1*, *PPARD*, *SERPINB2*, and *SLC12A6* [43]. In addition, a SNP in *GSTT1* predicted the frequency of neuropathy [44]. Another study was unable to find associations between 300,000 exome SNPs and thalidomide-related peripheral neuropathy [70]. Studies of lenalidomide, a sister drug of thalidomide with similar antiangiogenic immunomodulatory mechanisms of action, demonstrate significantly lower incidence of peripheral neuropathy [71]. The mechanism is hypothesized to be a PK effect similar to that observed with the platinum compounds; the half maximal inhibitory concentration (IC50) of lenalidomide is almost 500 times less than that of thalidomide (0.4 μmol/L vs. 194 μmol/L, respectively) [72]. This marked difference reflects the much lower serum concentrations of lenalidomide required for target activity in comparison with thalidomide and highlights the potency of lenalidomide.

Limitations of current studies

Biomarker discovery studies of CIPN have several limitations, the primary being a lack of an objectively assessable, universally accepted CIPN phenotype [73]. Varying methods to define the phenotypes, such as clinician-assessed National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) and grading classifications, have complicated the comparison of multiple study findings with one another. In addition, discordance across GWAS studies is a significant limitation [73]. Collapsing different phenotypes into a single definition may limit the ability to identify genetic predictor of any single phenotype. For instance, it is likely that a genetic predictor of neuropathic pain is distinct from a predictor of sensory versus motor neuropathy [74]. Failing to adjust for clinical (particularly cumulative dose received) or environmental differences may have impeded the precision of reported findings.

Data from patients treated with combination therapies rather than a single agent may have contributed to the inconsistent results across studies. While some SNPs may predispose patients to CIPN regardless of the neurotoxic agent, each class of agents, and perhaps each agent within that class, is likely to have independent risk factors. As one illustrative example, analyses have combined patients taking paclitaxel or docetaxel and included SNPs in *CYP2C8*, which is only involved in paclitaxel metabolism but not docetaxel [28]. Labeling how all taxanes are involved with CYP2C8 would not be appropriate.

A well-powered sample size is the cornerstone to the generation of valuable genetic association studies, granting the study enough power to confirm the correlations. Currently, most studies are retrospective in nature and are limited to the fixed sample size of the prospective study from which they were conducted, leading to underpowered analyses. Further, because a smaller number of toxicities occur in studies with smaller sample sizes, the ability to produce extensive data on toxicity for further analysis is restricted [73]. An additional factor to inspect is the genetic ancestry of the study population, reflected by distinct allele frequencies in the variations being investigated. Since these frequencies are due to the ancestral history of the populations, they must be accounted for in the association analyses. Otherwise, observed differences between those experiencing neuropathy and those who are not may simply be due to the ancestral composition of the compared groups rather than differences in chronic toxicities.

The reporting of genetic association studies should be as transparent as possible. The STrengthening and the REporting of Genetic Association Studies (STREGA) recommendations promote the transparency, excellence, and thoroughness of

genetic association study reporting [75]. Studies should also provide essential information such as quality error and call rates as they may have a significant effect on the ability to detect linkage or association.

Novel analytical approaches

Besides traditional approaches, analyses of gene expression (i.e., transcriptomics) or differential gene expression, protein expression (i.e., proteomics), or biochemical metabolite concentrations (i.e., metabolomics) may be useful for predicting future neuropathy occurrence, but data on applying these techniques to measure toxicity from cancer treatments is scarce [76]. Discovery-phase candidates from proteomic and metabolomic analyses require independent validation prior to translation into clinical practice.

Recent advances in human stem cell technology have allowed for increasingly detailed in vitro studies of CIPN. Adult human somatic cells (often skin fibroblasts or lymphocytes) can be reprogrammed into induced pluripotent stem cells (iPSCs) [77], which then may differentiate into specific cell types of interest. Neurons produced from these stem cell differentiation protocols allow researchers to harness human biology and genetics, including within specific patient populations such as patients with CIPN.

Future directions

To mitigate CIPN's detrimental impact on patient quality of life, a clear understanding of the molecular pathways underlying its development and natural history is necessary. This understanding will support the development of targeted clinical strategies [78]. Building on the foundational work done to date, the growth of novel research platforms will allow for new ways of interrogating these pathways. Table 2 provides a list of recommendations for future genetic studies of CIPN, which aim to ensure the translation of research findings into clinical decision-making. However, none of these biomarkers are currently ready to be translated into routine practice. To continue to make progress on understanding predictors of CIPN and predictors of response to various therapeutic strategies, the following strategies will be helpful: new methodological approaches to study genomics and molecular pathways, data sharing, and real-world data, as well as multidisciplinary funding and collaboration.

Table 2 Methodological recommendations for future research studies on biological predictors of CIPN

- ✓ Distinguishing the various phenotypes of CIPN (motor vs. sensory vs. neuropathic pain), in order to support consistency in the classification of "cases" across studies; studies may also want to target high-risk patients (e.g., patients who develop peripheral severe neuropathy after first few doses of treatment).
- ✓ Longitudinal assessment of CIPN, including pre-treatment assessment.
- ✓ Prospective research design is ideal, to ensure the collection of known relevant clinical factors including cumulative dose, drug exposure, diabetes, and race.
- ✓ Studies should clearly report the justification of genomic predictors interrogated.
- ✓ Consistent reporting of the process used for genotyping.
- ✓ Collaboration between study centers to increase sample size and confirm the generalizability of findings.
- ✓ Collaboration between patients, clinicians, and translational researchers will support the application of innovative methods to address clinically meaningful outcomes.
- ✓ Development and testing of interventions targeted at implicated pathways.

New methodological approaches from complex data analysis techniques can be applied to the intersecting effects of symptom biology. For instance, cluster analyses may include the impact of symptoms on the condition, manifestation of toxicities, and interaction of toxicities on the overall condition. Dissection of symptoms to underlying biology using genome-wide approaches can yield information on polymorphisms that may affect innate risk and response, as well as adaptive variability in gene expression resulting in individually dynamic pathobiology. Although genomic (genotyping, gene expression, and epigenetic) approaches are useful for dissecting effects and interactions of the tumor, treatment, and host susceptibility factors, these studies must involve a large number of subjects. As methodology improves power with smaller sample sizes, these studies may be linked with those conducted to examine primary mechanisms and toxicities [79].

To make significant progress in CIPN research, clinical research networks can be developed into data repositories where variable interactions such as pharmacogenomics, pharmacoproteomics, gene expression/proteomic changes in human specimens, and patient-reported outcomes can be linked to clinical phenotypes. This will ultimately move the field towards population-based rather than clinic-specific research, while encouraging standardization of data measures. Such networks are exemplified by NIH initiatives using public-private partnering mechanisms to provide publically available resources such as PhenX (the Phenotyping and Exposures project) and PROMIS (Patient-Reported Outcomes Measurement Information System).

Lastly, joint funding of proposals with a variety of funding agencies such as the National Cancer Institute, National Institute of Neurological Disorders and Stroke, and other research funders with overlapping missions has been considered an approach to leverage funds. Other examples of recent facilitation of larger scientific endeavors include the following: a growing investment in clinical research networks such as Patient-Based Research Networks; the linking of Clinical and Translational Study Award–supported academic sites; and complementary electronic resources, such as Clinical Research Networks. These encourage the expansion of current clinical research networks by conducting studies across

multiple research sites. Collaboration across sites through these mechanisms makes it feasible to increase sample size, increase generalizability, facilitate standardized data collection methods, and promote scientific exchange across programs and study sites.

Conclusions

A number of clinical and genetic predictors have been identified, yet we are still unable to adequately prevent or treat CIPN. Future work is needed to develop a CIPN risk model where the drug, genomic, and clinical data are incorporated to better understand the risk of various neurotoxic therapies. In summary, advances in research methodologies, new technologies, and creative partnering relationships enhance the feasibility of these proposed strategies through efficiency in conduct as well as the economy of funding.

Compliance with ethical standards

Conflict of interest This project was not specifically funded by any organization, but a couple of the investigators are generally funded by the National Institutes of Health/National Cancer Institute (R01CA211887, R01CACA189947)

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